May 12, 1999

VETERINARY SERVICES MEMORANDUM NO. 800.92

Subject: Compliance with 9 CFR 113.8, *In vitro* Tests for Serial Release

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics
Director, National Veterinary Services Laboratories

I. PURPOSE

The purpose of this memorandum is to remind all licensees and permittees of compliance issues concerning 9 CFR 113.8 and Veterinary Services Memorandum No. 800.90, to request all firms conducting *in vitro* potency tests for relative antigen content of inactivated products to submit an information summary on each of their *in vitro* reference preparations according to 9 CFR 116.5(a), and to clarify Center for Veterinary Biologics (CVB) policy concerning information that firms should provide on the APHIS Form 2008 when the results of such tests are reported according to 9 CFR 116.7.

II. BACKGROUND

The revised Standard Requirement (9 CFR 113.8) concerning the use of *in vitro* potency tests to determine the relative antigen content (potency) of a serial of inactivated veterinary biological product became effective May 19, 1997. Firms using immunoassays which did not meet this standard were given 2 years from the effective date of the final rule to comply with the revised requirements. Therefore, by May 19, 1999, all *in vitro* potency tests for relative antigen content should be conducted using unexpired immunogenic reference preparations in parallel line assays or other methods which demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay.

Veterinary Services Memorandum No. 800.90, issued August 5, 1998, provides guidelines for relative potency assays and reference preparations based on ELISA antigen quantitation and recommends procedures for satisfying the requirements in the regulations (9 CFR 113.8).

Since the publication of the August 5, 1998, memorandum, we have received requests from firms for further guidance on how to ensure the continuity of serial release actions after May 19, 1999. This memorandum addresses those requests.

III. GUIDELINES

After May 19, 1999, serials of inactivated product that are potency tested for release by *in vitro* procedures must be in compliance with 9 CFR 113.8. Serials not in compliance will not be released after May 19, 1999, unless CVB has granted the firm an extension of time for compliance and/or an exemption from the regulations to use other test methods that demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay.

Beginning May 19, 1999, CVB will require all firms to report on the APHIS Form 2008 the identity and expiration date of all reference preparations used in the *in vitro* testing of inactivated fractions of products so that CVB can determine that an approved unexpired reference preparation was used.

Data requested in the following information summary will assist CVB in tracking the status of approved reference preparations used for potency testing for serial release. By monitoring reference preparations in this manner, CVB will ensure that all *in vitro* tests for inactivated products are conducted with approved, unexpired, reference preparations and that plans are in place for the replacement of such reference preparations as they expire. Firms should submit the information summary and, when applicable, a request for an extension or exemption as described below, to CVB-LPD before the May 19, 1999, deadline. This will ensure the continuity of serial release actions and avoid possible delays that could occur if CVB has to review the firm's Outlines of Production and other records to verify compliance with 9 CFR 113.8.

A. Information Summary

All firms conducting *in vitro* potency tests to determine the relative antigen content of inactivated veterinary biological products, should submit a report on all of the *in vitro* reference preparations used by the firm in conducting these tests, with the following data for each reference preparation:

1. *Identification* - Identify each Master Reference and current Working Reference(s) as recorded in filed Outline(s) of Production and/or licensee or permittee records.

2. *Products Involved* - List the product code for each product for which the firm uses the designated reference preparation(s) to test for relative antigen content.

3. *Qualification Date* - Provide the date of manufacture, the date of initiation of the first efficacy trial, and the date of official correspondence from APHIS accepting the efficacy data qualifying and, if applicable, requalifying each designated reference preparation.

4. *Type of Data Provided* - Indicate the type of data the firm provided to APHIS to support qualification and or requalification of each designated reference preparation, i.e., "serology" or "host animal vaccination-challenge."

5. *Dating Period* - Indicate the dating period approved for each designated reference preparation.

6. *Storage Conditions* - Describe the conditions of storage for each designated reference preparation.

7. *Previous Extensions* - Provide the date of official correspondence from APHIS granting any previous extensions of the expiration date for each designated reference preparation.

8. *Expiration Date* - Indicate the date each designated reference preparation will expire.

9. *Test Procedures* - Identify the Outline of Production (Product Code) and/or special outline (number) that details the potency test procedure utilizing this reference preparation.

10. *Monitoring Procedures* - Describe the *in vitro* and/or *in vivo* test(s) used to monitor the stability of each designated reference preparation and the frequency of performing the test(s).

11. *Schedule for Replacement* - Briefly describe the schedule for replacement or requalification of each designated reference preparation.

12. *Initiation of Requalification* - Indicate the date that any requalification studies currently in process were initiated or are projected to be initiated.

B. Submission Procedures

CVB requests that firms submit three copies of this information summary to the Center for Veterinary Biologics-Licensing and Policy Development (CVB-LPD) before May 19, 1999. Firms should promptly update their data when reference preparations are

requalified, extended, or replaced with new reference preparations; provide CVB-LPD with three copies of the updated information; and submit appropriate outline changes to CVB-LPD that include the updated information.

C. Requests for Extensions and/or Exemptions

A request for an extension of time for compliance with the requirements in 9 CFR 113.8 should include an explanation of the difficulties encountered in producing and/or qualifying a reference preparation to demonstrate that the firm has made a good faith effort to achieve compliance with due diligence. A request for an exemption (i.e., permission to use alternatives to the procedures in 9 CFR 113.8 and Veterinary Services Memorandum No. 800.90) should include supplemental data demonstrating the scientific validity of alternate method(s). For either type of request, include an updated information summary for the reference preparations involved.

/s/ Thomas E. Walton for

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